

## EDITORIAL

## More light on QT interval measurement

L Toivonen

*Heart* 2002;87:193–194

The electrocardiographic QT interval can contain information on the risk of dying suddenly.

A prolonged QT interval signifies a delay in the ventricular repolarisation phase, which renders the heart vulnerable to malignant arrhythmias such as torsade de pointes ventricular tachycardia. This sign of disease is sometimes subtle and may avoid recognition unless meticulously sought. In this issue of *Heart*, Malik and colleagues<sup>1</sup> draw attention to methodological difficulties in the measurement of the QT interval.

The action potential duration of the myocardium, reflected as the QT interval on the surface ECG, depends on heart rate which hampers estimation of the intrinsic myocardial repolarisation time. The relation of the QT interval and heart rate, or cardiac cycle length, is modified by a number of physiologic processes. The mechanism causing the change in heart rate may variably influence ventricular repolarisation. For example, an equal increase in heart rate shortens the QT interval less during sympathetic stimulation by cold pressor test<sup>2</sup> and during cardiac pacing<sup>3</sup> compared to physical exercise. Furthermore, the response of the QT interval to a change in rate is not instantaneous, full adaptation taking 1–3 minutes.

#### CONTINUING DEBATE ON RATE CORRECTION OF QT INTERVAL

Several mathematical formulae have been utilised for rate correction of the QT interval. An inherent limitation is that they take only heart rate into consideration and miss all other determinants of the QT interval. Attempts to overcome this problem have included standardising the conditions under which the ECGs are undertaken. Different reference values have been proposed for diurnal periods and for the exercise test or its recovery period.<sup>4–5</sup> Analysis has also been limited to ECGs sampled only from periods of stable heart rate.<sup>6</sup> Even these attempts to eliminate confounders may be futile as Malik and colleagues<sup>1</sup> now report that the relation between QT interval and heart rate is highly individual. When they optimised the parabolic rate correction  $QT_c = QT/RR^\alpha$  for each individual, the exponent  $\alpha$  varied from 0.233 to 0.485 among 50 healthy persons. For comparison, the value for  $\alpha$  is 0.33 in Fridericia's and 0.50 in Bazett's equation.

Malik and colleagues conclude that correction of QT interval by any rate adjustment method may be fallacious. On the other hand, by examining the QT heart rate relation within a subject one could better estimate the intrinsic QT interval in that particular individual. However, there is no

evidence that such individual rate correction would improve discrimination of diseases such as hereditary long QT syndrome (LQTS). In addition, creating a formula for each individual would be cumbersome outside any research programme. The authors contribute to the widely accepted criticism of Bazett's equation, and recommend to discard it regardless of the circumstances. Other linear and non-linear formulae have been previously proposed,<sup>7–8</sup> none of which has gained general acceptance. What should the clinician then adhere to?

A limitation in the work of Malik and colleagues, which they also admit to, is that the individual QT–heart rate relation was examined in ambulatory conditions over a wide range of heart rates, and may not be representative for the rest electrograms. Actually most studies seeking optimal correction formulae have analysed rest ECGs in subject cohorts. From a practical point of view, a small deviation from true QT value would not invalidate non-ideal correction, since time to time variation in QT interval and measurement error are likely to be a greater source of inaccuracy.

#### WHAT IS THE AIM OF QT INTERVAL MEASUREMENT?

Heart rate correction of QT interval is applied for different purposes: to detect an abnormality in a subject and to evaluate the effect of interventions such as administration of a drug that prolongs QT interval. A clinician needs to judge whether an individual has hereditary LQTS or acquired long QT interval that causes potential clinical consequences. The latter condition occurs, for example, in cardiomyopathy, in bradycardia of complete heart block, and during electrolyte derangements, and is also induced by various cardiac and non-cardiac pharmaceuticals. Recent knowledge on ventricular repolarisation could help in understanding how to best identify these conditions.

Familial LQTS is caused by mutations in genes coding delayed rectifier potassium channels or sodium channels on myocyte sarcolemma.<sup>9</sup> In the most common subtype, LQT1, the slow potassium current  $I_{Ks}$  is defective, leading to inadequate shortening of QT interval during exercise. In another common subtype, LQT2, the defect is in the rapid potassium channel  $I_{Kr}$ , and in subtype LQT3 the sodium channel does not close adequately. In subtypes LQT2 and LQT3 the defects delay repolarisation more at long cycle lengths.<sup>10–11</sup> Accordingly, the QT interval lengthening is most obvious at slow heart rates in these genetic subtypes.<sup>5–12</sup> This is reflected in triggering of arrhythmias which occur at high heart rates of effort in LQT1 and at low heart rates during startling stimuli or rest in the two other subtypes.<sup>13</sup>

Correspondence to:  
Lauri Toivonen, MD,  
Division of Cardiology,  
Helsinki University Central  
Hospital, Haartmaninkatu  
4, PO Box 340, FI-00029  
HUS, Helsinki, Finland;  
lauri.toivonen@hus.fi

Most antiarrhythmic drugs that prolong QT interval block IKr potassium channels,<sup>14</sup> as do the majority of non-cardiac drugs like terfenadine, thioridazine, and erythromycin. The IKr blockers sotalol and dofetilide show reverse use dependence—that is, they lengthen repolarisation more at a slow rate. Furthermore, in cardiomyopathy<sup>15</sup> and severe bradycardia<sup>16</sup> IKr channels are downregulated, and also hypokalaemia inhibits IKr function. Consequently, in many acquired states the QT interval prolongation would accentuate at resting heart rates. Also in LQT1 subtype the QT interval prolongation is enhanced when heart rate decelerates after exercise.<sup>5</sup> Thus in most clinical conditions the QT interval prolongation is best recognisable at slow heart rate and bradycardia. In contrast, ECGs sampled at elevated rates would contain less information and raise problems of inaccurate heart rate correction.

The QT–heart rate relation is different between genetic subtypes of LQTS. Malik and colleagues demonstrate that the QT–heart rate relation varies widely also between healthy subjects, to a greater extent than previously presumed, and speculate that subtle differences in integrated function of sarcolemmal ion channels might be common. A question arises as to whether the QT–heart rate relation would characterise arrhythmia risk in heart diseases or predict risk of proarrhythmic drug responses. The new observations contribute most to QT interval analysis in scientific research on physiologic and pathologic phenomena, including the action of pharmaceuticals. Guidelines of the European Society of Cardiology<sup>14</sup> give instructions on how to evaluate proarrhythmic potential in the development of pharmaceuticals, and also provide insight for clinicians to estimate patient safety while using QT prolonging drugs.

### MINIMISE THE NEED FOR RATE CORRECTION

Some suggestions and precautions for QT interval measurement are listed in the box below. A discrete U wave after the T wave has returned to baseline should be excluded from measurement. When T and U waves are fused the U component should be included, although the numerical value of “QTU interval” is not crucial since repolarisation would in any case be abnormally delayed. By which algorithm to rate-correct remains open. Malik and colleagues found the individually optimised exponent  $\alpha$  to be 0.37 on average, not far from 0.33 for  $\alpha$  in the Fridericia’s cubic root correction equation. Applied to rest ECGs of a cohort, Fridericia’s formula yields less residua compared to Bazett’s square root formula,<sup>7</sup> and therefore might be preferable for clinical practice. Comparing QT interval to a nomogram of QT intervals in a normal population might eliminate need for any rate adjustment.<sup>17</sup> With this method, normality could be judged by percentile deviation from normal cohort, for which sufficiently large databases have not yet been created. Since most clinically important information on QT interval duration is found at slow heart rates, electrograms should be undertaken when the subject is at complete rest.

The QT intervals vary widely between LQTS patients carrying even the same mutation, notably overlapping with the QT intervals of non-carriers,<sup>18</sup> implying that measurement of QT interval alone from rest ECG cannot ever provide a diagnosis in all cases of inherited LQTS. Fortunately, the risk of life threatening arrhythmias is low in LQTS gene carriers who have normal QT interval, but does exist, at least in the presence of strong triggers. Measurement of QT interval in close relatives and analysis of dynamic features of QT interval during exercise test or ambulatory electrocardiography might facilitate clinical diagnosis in subjects with borderline QT interval lengthening.

### Recommendations for QT interval measurement in the clinic

- Record the ECG in normal physiologic state (avoiding post-prandial period)
- Allow a few minutes rest to adapt QT interval to heart rate
- Measure QT interval from more than one lead, preferably leads II and V3–V5
- Eliminate separate U wave but accept T–U fusion in measurement
- Measure at least 3–5 cardiac cycles
- Avoid cardiac cycles with large sinus interval variation or preceded by arrhythmias
- Use a formula to correct QT interval (that is, adjust to rate 60 beats/minute)
- May use exercise test to observe accentuated QT lengthening at recovery

### REFERENCES

- 1 **Malik M**, Färholm P, Batchvarov V, *et al*. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. *Heart* 2002;**87**:220–8.
- 2 **Davidowski TA**, Wolf S. The QT interval during reflex cardiac adaptation. *Circulation* 1984;**69**:22–5.
- 3 **Akhras F**, Richards AF. The relationship between QT interval and heart rate during physiologic exercise and pacing. *Jpn Heart J* 1981;**63**:481–6.
- 4 **Browne KF**, Prystowsky E, Heger JJ, *et al*. Prolongation of the QT interval during sleep in man. *Am J Cardiol* 1983;**52**:55–9.
- 5 **Swan H**, Viitasalo M, Piippo K, *et al*. Sinus node function and ventricular repolarization during exercise stress test in long QT syndrome patients with KVLQT1 and HERG potassium channel defects. *J Am Coll Cardiol* 1999;**34**:823–9.
- 6 **Viitasalo M**, Karjalainen J. QT intervals at heart rates from 50 to 120 beats per minute during 24-hour electrocardiographic recordings in 100 healthy men: effects of atenolol. *Circulation* 1992;**86**:1439–42.
- 7 **Puddu PE**, Jouve R, Mariotti S, *et al*. Evaluation of ten QT prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic-root Fridericia’s equation. *J Electrocardiol* 1988;**21**:219–29.
- 8 **Sagie A**, Larson MG, Goldberg RJ, *et al*. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol* 1992;**70**:797–801.
- 9 **Towbin JA**, Vatta M. Molecular biology and the prolonged QT syndromes. *Am J Med* 2001;**110**:385–98.
- 10 **Schwartz PJ**, Priori SG, Locati EH, *et al*. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na<sup>+</sup> channel blockade and to increases in heart rate. Implications for gene-specific therapy. *Circulation* 1995;**92**:3381–6.
- 11 **Priori SG**, Napolitano C, Cantù F, *et al*. Differential response to Na<sup>+</sup> channel blockade,  $\beta$ -adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. *Circ Res* 1996;**78**:1009–15.
- 12 **Stramba-Badiale M**, Priori SG, Napolitano C, *et al*. Gene-specific differences in the circadian variation of ventricular repolarization in the long QT syndrome: a key to sudden death during sleep? *Italian Heart Journal* 2000;**1**:323–8.
- 13 **Schwartz PJ**, Priori SG, Spazzolini C, *et al*. Genotype-Phenotype correlation in the long QT syndrome. Gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;**103**:89–95.
- 14 **Haverkamp W**, Breithardt G, Camm AJ, *et al*. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. *Eur Heart J* 2000;**21**:1216–30.
- 15 **Huang B**, Qin D, El-Sherif N. Early down-regulation of K<sup>+</sup> channel genes and currents in the postinfarction heart. *J Cardiovasc Electrophysiol* 2000;**11**:1252–65.
- 16 **Volders PG**, Sipido KR, Vos MA, *et al*. Downregulation of delayed rectifier K<sup>+</sup> currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. *Circulation* 1999;**100**:2455–61.
- 17 **Karjalainen J**, Viitasalo M, Mänttari M, *et al*. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. *J Am Coll Cardiol* 1994;**23**:1547–53.
- 18 **Piippo K**, Swan H, Pasternack M, *et al*. A founder mutation of the potassium channel KCNQ1 in long QT syndrome. *J Am Coll Cardiol* 2001;**37**:562–8.